filed on 1/12/2000. The Examiner stated that this Application now complies with the requirements of 37 C.F.R. §1.824.

The Examiner acknowledged applicants' election with traverse of Group IX in Paper No. 7 filed on August 5, 1999. The Examiner stated that the traversal is on the ground that the inventions of Groups VIII, IX and X are all drawn to methods of inhibiting inflammation in a subject by administering a compound that is capable of interfering with the interaction between EN-RAGE peptide and RAGE, and that there would not be an undue burden on the Examiner to search these three groups together. The Examiner stated that this traversal is found persuasive in part, further stating that even though these three groups are all directed to methods of inhibiting inflammation, the agents or compounds used (anti-EN-RAGE antibodies, peptides or nucleic acid molecules), are patentably distinct and fall into different classes and subclasses, and a search of one will not necessarily reveal pertinent art on the others. However, the Examiner reconsidered the restriction and decided to examine Groups VIII and IX, (i.e. the method of inhibiting inflammation in a subject by administering a peptide, and the method of inhibiting inflammation in a subject by administering anti-EN-RAGE antibodies) together. The Examiner stated that Group X will not be examined.

The Examiner stated that the restriction requirement is still deemed proper and is therefore made final.

The Examiner withdrew claims 10-46, 53 and 69 from consideration as drawn to non-elected inventions.

Thus, the Examiner stated that Group VIII (claims 47-48, 50-52, 54-68) and Group IX (claims 47, 49-51, 54-68) are pending and under consideration by the Examiner. Upon entry of the present amendment, claims 47-52, and 55-68 will now be pending and under examination in the subject application.

Specification

The Examiner stated that a new title of the invention is required because the word "novel" is not considered as part of the title of an invention, adding that the Patent and Trademark Office does not include such words at the beginning of the invention. The Examiner suggested that the word "novel" be deleted from the title of the invention. The Examiner directed applicants to see M.P.E.P. § 606.01.

In response, applicants respectfully traverse the Examiner's requirement that a new title of the invention be provided. The Examiner has taken the position that the word "novel" is not considered as part of the title of an invention, that the Patent and Trademark Office does not include such words at the beginning of an invention, and that the word "novel" therefore should be deleted. In support of this assertion, the Examiner directed applicants to see M.P.E.P. § 606.01. Applicants respectfully point out that M.P.E.P. § 606.01 does not support the Examiner's position that the word "novel" is not considered as part of the title of an invention. Rather, M.P.E.P. § 606.01 recites in pertinent part, "[i]nasmuch as the words 'improved,' 'improvement of,' and 'improvement in' are not considered as part of the title of an invention, the Patent and Trademark Office does not include <u>these words</u> at the beginning of the title of an invention" (emphasis added). Moreover, applicants note that the United

States Patent and Trademark Office has in fact issued more than 5,400 patents since 1976 in which the word "novel" appears in the title, several of these patents issuing as recently as September 19, 2000. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the requirement that applicants provide a new title of the invention.

Claim objections

The Examiner objected to claim 54 because it is dependent on non-elected claim 26.

In response, applicants have hereinabove canceled claim 54 without prejudice to applicants' right to pursue the subject matter of the claim in a future divisional or continuation application.

Claim Rejections - 35 U.S.C. § 112

The Examiner rejected claims 47-52 and 54-68, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting inflammation in a subject by administering soluble RAGE peptide (sRAGE), anti-RAGE or anti-EN-RAGE antibodies, does not reasonably provide enablement for a method of inhibiting inflammation in a subject by administering to said subject "all" possible compounds, or "all" possible peptides, or "all" possible antibodies and fragments thereof, that interfere with the interaction between EN-RAGE and its receptor. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Examiner stated that Claim 47 recites "a method for inhibiting inflammation in a subject which comprises administering to the subject a compound capable of interfering with the interaction between EN-RAGE peptide and RAGE...". and claims 51 and 52 recite "...wherein the compound is a peptide, and wherein the peptide is an antibody or a fragment thereof..." respectively, while the specification discloses that in a mouse model of delayed hypersensitivity (DH), administration of sRAGE suppressed inflammation upon injection of methylated BSA (mBSA) into the foot pad of mice previously-sensitized with mBSA over the lymph nodes, in a dose-dependent manner, (see page 33, lines 28 through page 34 line 9, and figure 4). The Examiner stated that in the same model, the development of inflammation was also considerably suppressed with either anti-EN-RAGE$(ab')_2$, or anti-RAGE$(ab')_2$ and when mice were treated with both anti-EN-RAGE and anti-RAGE F $(ab')_2$, even further suppression of the inflammatory response was observed, (page 34, line 1 9 and figure 4). The Examiner stated that figure 4 shows that sRAGE, anti-EN-RAGE F $(ab')_2$, or anti-RAGE F $(ab')_2$, all inhibit inflammation of the mouse model of delayed hypersensitivity, however, the instant specification does not illustrate whether this inhibition is because these agents interfere with the interaction between EN-RAGE and RAGE. The Examiner stated that in the mouse model of delayed hypersensitivity, inflammation is induced by injecting the mice with mBSA not by injecting the mouse with EN-RAGE, therefore, there is no correlation between inflammation and EN-RAGE. The Examiner stated that instant specification fails to establish a nexus between the interaction of En-RAGE with RAGE and inflammation. The Examiner stated that since RAGE is known to have other ligands, the possibility exists that sRAGE, and anti-RAGE F$(ab')_2$ interfere with the interaction between RAGE and

"any" one of its ligands, including EN-RAGE. The Examiner stated that the instant specification does not demonstrate that sRAGE, or anti-RAGE $F(ab')_2$ exclusively interfere with the interaction between EN-RAGE-RAGE, and by doing so inhibit inflammation. Thus, the Examiner stated that the instant specification is only enabling for a method of inhibiting inflammation in a subject by administering anti-EN-RAGE, and does not reasonably provide enablement for a method of inhibiting inflammation in a subject by administering to said subject "all" possible compounds, "all" possible peptides, or "all possible antibodies, that may interfere with the interaction between RAGE and its receptor. The Examiner stated that by application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, in the instant application, the quantity of experimentation to determine which of the limitless possible compounds, peptides and antibodies, would interfere with the interaction between EN-RAGE and its receptor, is practically infinite and the guidance provided in the specification very little. The Examiner stated that the instant claims are not limited to naturally-occurring compounds and the instant specification does not provide examples of representative compounds that interfere with the interaction of EN-RAGE and its receptor. The Examiner stated that anti-EN-RAGE and anti-EN-RAGE $F(ab')_2$ fragment are the only peptides disclosed in the instant

specification that interfere with the interaction between EN-RAGE and RAGE. The Examiner stated that soluble RAGE and anti-RAGE antibodies would interfere with the interaction of RAGE and any of its ligands. The Examiner stated that absent further guidance from the specification it would constitute undue experimentation to determine all the other compounds that might interfere with the interaction between EN-RAGE and RAGE, as is encompassed by the scope of the claims. The Examiner stated that as such, claims 47-50-52 and 54 are not commensurate in scope with the specification but rather are broader than the supporting disclosure.

The Examiner stated that with respect to claims 55, 60, 67 and 68, which recite "...wherein the inflammation is associated with delayed hypersensitivity, accelerated atherosclerosis, lupus, septic shock, endotoxemia, autoimmune, bacterial-associated or other pathogen-associated infection", the instant specification is non-enabling for a method of treatment for any of the recited diseases, and is only enabling for a method of inhibiting inflammation associated with delayed hypersensitivity, (see page 33, lines 28 through page 34 line 9, and figure 4). The Examiner stated that the instant specification provides no disclosure that EN-RAGE/RAGE interaction is involved in accelerated atherosclerosis, lupus, septic shock, endotoxemia or bacterial-associated or other pathogen-associated infection, neither does it demonstrate that interfering with the interaction between EN-RAGE and RAGE would inhibit any of these diseases. The Examiner stated that absent further guidance from the specification it would constitute undue experimentation to determine if all the recited diseases are induced by the interaction between EN-RAGE and RAGE, and if so, if blocking this interaction would inhibit

these diseases. Therefore, the Examiner stated that the instant specification is only enabling for a method of inhibiting inflammation by administering anti-EN-RAGE antibodies or anti-EN-RAGE $F(ab')_2$ fragment said anti-EN-RAGE antibodies interfering with the interaction between EN-RAGE and RAGE.

The Examiner stated that with respect to claim 64, the instant specification is non-enabling for a method of treatment, wherein the carrier comprises virus, or retro viral vector, there are no examples where either a virus or a retro viral vector was used as a carrier for sRAGE, anti-RAGE or anti-EN-RAGE antibodies. Furthermore, it would be unpredictable if said vector or virus would make practical or safe carriers.

The Examiner stated that Claims 54, 56-59, 61-66 are rejected under 35 U.S.C. 112, first paragraph insofar as they depend on claim 47 for the limitations set forth directly above in this paragraph.

The Examiner stated that with respect to claim 47 which recites "a method for inhibiting inflammation in a subject which comprises administering to the subject a compound *capable* of interfering with the interaction between EN-RAGE and its receptor...", the specification is non-enabling for a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that does not interfere with the interaction between RAGE and its receptor, and is only capable of interfering if further modified, since applicants have not taught how to further modify said compound such that it can interfere with the interaction between RAGE and its receptor. The Examiner stated that it has been held that an element is

"capable of" performing a function is not a positive limitation but only requires the ability to perform. The Examiner stated that it does not constitute a limitation in any patentable sense. The Examiner directed applicants to see In re Hutchison, 69 USPQ 138.

In response, applicants respectfully traverse the rejection of claims 47-52, and 54-68 under 35 U.S.C. §112, first paragraph. Applicants acknowledge Examiner's statement that the specification is enabling for "a method of inhibiting inflammation in a subject by administering anti-EN-RAGE." Moreover, applicants maintain that the presently claimed invention is fully enabled by the specification. Applicants' claimed invention is directed to, *inter alia*, a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that interferes with the interaction between extracellular novel RAGE binding (EN-RAGE) peptide and receptor for advanced glycation endproduct (RAGE) in the subject thereby inhibiting inflammation in the subject.

Applicants maintain that the claimed invention is fully described in the specification and that one of ordinary skill in the art could make and use the invention without undue experimentation. In support of this contention, applicants point out that the subject specification includes examples as well as a sufficient and enabling description. For example, pages 27-35 of the specification encompass a discussion of the experimental details for carrying out the claimed invention for several particular embodiments. Applicants respectfully point out that the M.P.E.P. provides that "because only an enabling disclosure is required, applicant need not describe <u>all actual embodiments</u>." (Emphasis

added). Applicants point out that the examples presented along with the description would allow one skilled in the art to practice the claimed invention without undue experimentation.

In that regard, applicants first respectfully disagree with Examiner's statements that "there is no correlation between inflammation and EN-RAGE" and that the "instant specification fails to establish a nexus between the interaction of EN-RAGE with RAGE and inflammation." Applicants provide ample evidence that the EN-RAGE-RAGE interaction indeed plays a role in inflammation. Specifically, Example 1 in the Experimental Details section of the specification (page 27, line 13 through page 35, line 17) provides data that show that EN-RAGE:RAGE interaction activates cells, such as endothelial cells, which are importantly involved in the inflammatory response. (See, in particular, the specification, at page 28, lines 26-35). Moreover, the specification provides specific examples of controlled experiments, as Examiner notes, which show that in an inflammation model, when the interaction between EN-RAGE and RAGE is blocked, either by blocking RAGE with an anti-RAGE or by blocking EN-RAGE with an anti-EN-RAGE, inflammation is significantly decreased or inhibited as compared with the administration of a control. When both RAGE and EN-RAGE are blocked, inhibition occurs to an even greater degree. Contrary to the Examiner's statements, applicants maintain that the data presented, therefore, do establish a correlation between EN-RAGE-RAGE interaction and inflammation. Moreover, Examiner's acknowledgement, noted above, that the invention is enabling for "a method of inhibiting inflammation in a subject by

administering anti-EN-RAGE" supports such a correlation.

With regard to Examiner's position that sRAGE or anti-RAGE $F(ab')_2$ are not shown to exclusively interfere with the interaction between EN-RAGE and RAGE, applicants contend that the Examiner has introduced an irrelevancy into the enablement determination. Applicants claimed invention is directed to, *inter alia*, a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that interferes with the interaction between extracellular novel RAGE binding (EN-RAGE) peptide and receptor for advanced glycation endproduct (RAGE) in the subject thereby inhibiting inflammation in the subject. As discussed hereinabove, applicants have provided several examples demonstrating both that the EN-RAGE-RAGE interaction plays a role in inflammation and that interfering with that interaction by administering a compound does in fact inhibit inflammation. These examples further demonstrate, therefore, that a compound that interferes with the EN-RAGE-RAGE interaction will necessarily inhibit inflammation. Whether such a compound also inherently interferes with another interaction is not relevant to the enablement of the presently recited claims.

Moreover, the Examiner expresses the position that because the specification does not disclose non-naturally occurring compounds that interfere with the interaction between RAGE and EN-RAGE, the specification is therefore not enabling for the inhibition of inflammation by administering such non-naturally occurring compounds.

Applicants direct Examiner's attention to M.P.E.P. §2164.08,

which states that "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." Moreover, M.P.E.P. §2164.04 states that "[i]n order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. The court in In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), further stated that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

In the instant application, applicants contend that a reasonable correlation exists between the results expected from the administration of non-naturally occurring compounds based on the examples of compounds provided in the specification. There is no reason to believe, and the Examiner provides no such reason or supporting evidence, that non-naturally occurring compounds which interfere with the interaction would not inhibit inflammation. On the contrary, one with ordinary skill in the art would reasonably and clearly expect that any compound that interferes with the RAGE-EN-RAGE interaction would, like a non-

naturally occurring compound, necessarily inhibit inflammation. Accordingly, the Examiner has not met the required burden as described in the M.P.E.P. and reiterated above.

Likewise, applicants need not disclose examples of every disease in which inflammation occurs in order to enable the present claims as written. One of ordinary skill in the art would have no reason to believe that inflammation associated with the diseases and disorders as recited in the present claims would not be effectively treated by the administration of a compound that inhibits interaction of EN-RAGE and RAGE.

Moreover, applicants maintain that vectors and viruses are recognized in the art as acceptable carriers. The Examiner's position that it is unpredictable whether such vectors or viruses would be suitable is not supported by evidence to cast doubt on the objective truth of the applicants statement as required and stated in M.P.E.P.

Finally, with regard to Examiner's position that "capable of" is not a positive limitation, applicants, without conceding the correctness of Examiner's position, but to advance prosecution of the subject application, have hereinabove amended claim 47 to recite "a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that interferes with the interaction between extracellular novel RAGE binding (EN-RAGE) peptide and receptor for advanced glycation endproduct (RAGE) in the subject thereby inhibiting inflammation in the subject."

Applicants maintain that the scope of enablement in the subject

application bears a reasonable correlation to the scope of the claims. Applicants moreover maintain that the Examiner has not met the required burden to establish a reasonable basis to question the enablement provided for the claimed invention. Accordingly, applicants maintain that the invention is fully enabled by the specification, and respectfully request that the Examiner reconsider and withdraw the above rejection under 35 U.S.C. 112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner stated that Claims 47-52, 54-68 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that Claims 47-48, 50, recite the acronym "EN-RAGE", and claims 49-50 recite the acronym "sRAGE", the recitation of these acronyms render these claims unclear and confusing. The Examiner stated that Applicants are advised to recite the full names of the peptides in the first independent claim to obviate this rejection.

The Examiner stated that Claim 50 recites "...wherein the compound *consists essentially* of the ligand binding domain of sRAGE or EN-RAGE...", however, it is unclear if the entire ligand binding domain of EN-RAGE or that of sRAGE is *essential* for the claimed compound or if only some parts of the domains are essential? The Examiner stated that what else should the claimed compound consist of? The Examiner stated that clarification of this claim is required.

The Examiner stated that Claims 49, 51 and 54-68 are rejected as being vague and indefinite insofar as they depend on claim 47 for the limitations set forth directly above.

In response, without conceding the correctness of Examiner's position but to advance prosecution of the subject application, applicants have amended claim 47 to recite the full names of the peptides "RAGE" and "EN-RAGE".

With regard to the language "consisting essentially of", applicants respectfully traverse this ground of rejection. Applicants maintain that the claim is clear and definite as written. The scope of the claim as written encompasses the specified materials (the respective ligand binding domains) and those that do not materially affect the basic and novel characteristics of the claimed invention. Accordingly, applicants respectfully request that Examiner reconsider and withdraw the rejection under 35 U.S.C. 112, second paragraph.

Claim rejections-35 U.S.C. § 103

The Examiner rejected claims 47-52, 56-59, 61-66 under 35 U.S.C. 103(a) as being unpatentable over Hori et al (08/95), or Morser et al (US Patent 04/96) in view of Ritthaler et al (1995).

The Examiner stated that Hori et al. disclose two ligands (a 12 kDa peptide and amphoterin), that bind to RAGE, and show that sRAGE and anti-RAGE $F(ab)_2$ antibodies block the interaction between RAGE and amphoterin, (see abstract). The Examiner stated that Hori et al. demonstrate that amphoterin binds RAGE with higher affinity than AGEs, they also show that RAGE has physiologically relevant ligands distinct from AGEs which are

involved in physiologic processes other than diabetes and accumulations of AGE (abstract and page 25754, lines 1-6).

The Examiner stated that Morser et al. teach a soluble human RAGE (sRAGE) and antibodies to RAGE that inhibit the ability of ligands (such as AGEs and amphoterin) to bind to RAGE, said sRAGE or antibodies bieng useful for disorders or symptoms which result from the association between RAGE and its ligands. (Column 6, lines 53-56 and column 11, lines 53-56). The Examiner stated that Morser et al. also disclose methods of treatment for pathological disorders involving RAGE, by administering orally, intravenously, intra peritoneally or intramuscularly, an effective amount of sRAGE or anti-RAGE antibodies to a mammal, (column 19, lines 10-24 column 19, lines 56-60). However, the Examiner stated that neither Hori et al, nor Morser et al disclose a method of inhibiting inflammation by administering a compound that interferes with the interaction between RAGE and EN-RAGE.

The Examiner stated that Ritthaler et al. disclose that the interaction of AGEs and RAGE may contribute to the development of vascular lesions and that examination of human atherosclerotic plaques or experimentally induced inflammatory lesions in response to local instillation of AGEs, showed prominent accumulation of cells strikingly positive for RAGE, (see abstract and page 688, column 2), thus implying that RAGE is involved in inflammation.

Therefore, the Examiner stated that it would have been prima facie obvious at the time of the invention to devise a method of inhibiting inflammation by administering the sRAGE or the anti-

RAGE antibodies disclosed by Hori et al or Morser et al, because both Hori and Morser references demonstrate that sRAGE and anti-RAGE antibodies block the interaction between RAGE and its ligands, and, Ritthaler et al teach that RAGE and its ligands are involved in inflammation. The Examiner stated that with respect to claims 58 and 59 which recite specific dosage of the claimed compound to be administered, and the schedule of administering said compound, respectively, it would have been obvious to one of skill in the art to optimize the dosage and the schedule of administering the sRAGE and anti-RAGE antibodies taught by Hori or Morser, to get the most benefit for each patient. The Examiner stated that one of ordinary skill in the art would have been motivated to formulate a method of treatment for inflammation using the sRAGE or the anti-RAGE antibodies taught by Hori et al or Morser et al., because it is always desirous to develop a good therapy for inflammation and Ritthaler et al showed that RAGE and its ligands may play a role in inflammation.

The Examiner stated that no claim is allowed.

In response, applicants respectfully traverse the rejection of claims 47-52, 56-59, 61-66 under 35 U.S.C. 103(a) as being unpatentable over Hori et al. (08/95), or Morser et al (US Patent 04/96) in view of Ritthaler et al (1995). Applicants' claimed invention is directed to, *inter alia*, a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that interferes with the interaction between extracellular novel RAGE binding (EN-RAGE) peptide and receptor for advanced glycation endproduct (RAGE) in the subject thereby inhibiting inflammation in the subject. Applicants maintain that the cited references, either alone or in combination do not

render applicants' claimed invention obvious.

Applicants respectfully direct Examiner's attention to M.P.E.P. §2142, which states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some motivation or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations. Applicants maintain that Examiner has not established a *prima facie* case of obviousness based on these criteria.

There clearly is no motivation or suggestion in the references to modify or combine the references to arrive at the applicants' claimed invention.

Hori, et al. merely provides a general statement that RAGE has physiologically relevant ligands distinct from AGEs which are likely, via their interaction with the receptor to participate in physiologic processes outside of the context of diabetes and accumulation of AGEs. There is no mention of what such physiological processes might be, nor is there any suggestion of the existence of EN-RAGE, the novel peptide disclosed in the subject application and recited in the present claims. The fact that many ligands may exist does not make obvious the discovery of a particular novel EN-RAGE.

Ritthaler, et al does not remedy the deficiencies of Hori, et al.

Ritthaler does not contemplate EN-RAGE and therefore cannot contemplate the claimed invention which is directed to, *inter alia*, a method for inhibiting inflammation in a subject which comprises administering to the subject a compound that interferes with the interaction between extracellular novel RAGE binding (EN-RAGE) peptide and receptor for advanced glycation endproduct (RAGE) in the subject thereby inhibiting inflammation in the subject. There clearly is no motivation, therefore, to modify or combine Hori and Ritthaler to arrive at the claimed invention.

Similarly, there is no motivation to combine Morser with Ritthaler to arrive at the applicants' claimed invention. Neither reference suggests inhibiting inflammation in a subject by administering a compound that inhibits the interaction between RAGE and the novel peptide EN-RAGE.

Even following the logic of the Examiner in combining the cited references, but without conceding the correctness of this logic, one would not arrive at the claimed invention. The third criteria necessary to establish a prima facie case of obviousness clearly is not satisfied as none of the references teach EN-RAGE and, therefore, the references in combination do not suggest treating inflammation by administering a compound that interferes with the RAGE-EN-RAGE interaction.

Applicants therefore maintain that the references cited by the Examiner, either alone or in combination, do not render obvious applicants' claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 47-52, 56-59, 61-66 under 35 U.S.C. 103(a).